Chapter 4

Pleiotropic Functions of HTLV-1 Tax Contribute to Cellular Transformation

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1. Introduction

Human T cell leukemia virus type-1 (HTLV-1) is the only retrovirus known to be the etiologic agent of a human cancer, adult T-cell leukemia/lymphoma (ATLL), a highly aggressive cancer of mature T cells. Epidemiological reports suggest that 10 to 20 million people throughout the world are infected with HTLV-1, which is endemic in parts of sub-Saharan Africa, the Caribbean, Japan, and South America [1]. HTLV-1 encodes a regulatory protein, Tax, which is essential for virus replication and plays a significant role in the oncogenic potential of HTLV-1. This chapter will summarize the effects of Tax on cellular processes including transcription, cell cycle checkpoints, and DNA repair, and will discuss how these activities may contribute to its transforming potential.

2. HTLV-1 epidemiology and pathogenesis

HTLV-1 is a type C, complex, enveloped retrovirus belonging to the family *Retroviridae* and the genus deltaretrovirus. This genus includes three additional HTLV members (HTLV-2, -3, and -4), and two non-human members, bovine leukemia virus (BLV), and simian T cell leukemia virus (STLV). HTLV-1 was originally isolated from a patient diagnosed with cutaneous T cell lymphoma, and was subsequently shown to be the causative agent of ATLL [2-4]. HTLV-1 is also recognized as the etiologic agent of a neurodegenerative disease, tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM), that affects the central nervous system [5,6]. The route of HTLV-1 transmission influences its pathogenesis. Sexual transmission, which occurs most efficiently from males to females, IV drug use, and blood transfusions are typically associated with the

development of TSP/HAM, whereas the most common route of transmission, mother to child, is preferentially associated with the development of ATLL [7-12].

ATLL, a rapidly progressing cancer of mature $CD4^+$ T cells, has been classified into four clinical subtypes:, smoldering, chronic, lymphoma, and acute [13]. Leukemic cells from ATLL patients have a phenotype of $CD2^+$, $CD3^+$, $CD4^+$, $CD8^-$, and $HLA\text{-}DR^+$, express high levels of interleukin 2 (IL-2) and its receptor (IL-2R), and frequently have lobulated nuclei, causing them to be referred to as flower cells. Interestingly, these cells are only moderately responsive to IL-2, and HTLV-1 infected T cells proliferate continuously in the absence of exogenous IL-2, a characteristic associated with late stage T-cell transformation [14]. Other members of the deltaretrovirus family have also been linked to proliferative diseases. For instance, sheep infected with BLV develop B-cell leukemia/lymphoma, and the simian counterpart of HTLV-1, STLV-1, induces an ATLL like disease in African green monkeys [15,16]. In contrast, HTLV-2 has not been definitively linked to human cancer and the disease potentials of the newly discovered HTLV-3 and -4 viruses remain unknown [17,18].

2.1. HTLV-1 genome

The HTLV-1 proviral genome is approximately 9 kb in length including flanking long terminal repeats (LTR) composed of U3, R, and U5 regions. HTLV-1 encodes structural (*gag*, *env)* and enzymatic (*pro*, *pol)* genes typical of all retroviruses. In addition, a highly conserved p*X* region located near the 3′ LTR, encodes four open reading frames (ORFs) that produce regulatory proteins [19,20]. ORF I encodes p12, which undergoes proteolytic cleavage to generate p8. Alternative splicing of ORF II produces the p13 and p30 proteins. Analysis of full-length infectious molecular clones of HTLV-1 containing mutations in p12, p13, and/or p30 in a rabbit infection model demonstrated an important role for these viral accessory proteins in establishing and maintaining viral persistence [21-26]. ORFs III and IV produce doubly spliced mRNA encoding Rex and the viral oncoprotein Tax, respectively. These proteins differentially regulate transcription, which is essential for viral replication [26-29]. Rex is a 27 kDa protein that regulates post-transcriptional viral gene expression by transporting unspliced mRNA from the nucleus to the cytoplasm and increases viral RNA stability, potentially influencing latent and productive phases of the virus life cycle [26,29]. Tax is a potent transcriptional regulator of viral and cellular gene expression and modulates cellular protein function. Unlike Tax, HBZ is transcribed from the antisense strand of the proviral genome and appears to be constitutively expressed in HTLV-1-infected and ATLL cells [30]. HBZ promotes the proliferation of human T cells and may play an important role in maintaining malignant transformation of HTLV-1 infected T cells [31]. The mechanisms of Tax-mediated cellular transformation will be discussed below.

2.2. Transformation by HTLV-1

Multiple studies have demonstrated that Tax is sufficient for cellular transformation and is important for HTLV-1 mediated tumorigenesis [32-38]. Acute transforming retroviruses rapidly induce tumors by expressing a viral oncogene [39]. In contrast, chronic transforming retroviruses induce tumors at a much slower rate by aberrantly regulating genes upstream or

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downstream of the proviral insertion site [40]. Neither of these models explains HTLV-1 mediated transformation since no cellular homologue of Tax has been identified and HTLV-1 integration is random. The oncogenic potential of Tax has been extensively characterized in rodent fibroblast cell culture systems, transgenic mouse models, and immortalization and transformation studies in primary human T cells.

One of the first studies to show that Tax could independently transform human T cells used a transformation–defective but replication competent *herpes saimiri* vector encoding Tax to infect primary cord blood lymphocytes [32]. The transformed T cells were $CD4^+/CD8^-$ and expressed high levels of IL-2R, resulting in clonally expanded cell populations similar to ATLL cells. Deletion of the Tax gene in this vector eliminated its transforming potential [32]. In addition, a replication defective HTLV-1 provirus isolated from leukemic cells of an ATLL patient expressed Tax and promoted loss of contact inhibition and anchorage-independent growth in rodent fibroblasts [37]. Mutation of the Tax gene in this proviral vector reduced tumor formation in nude mice, suggesting that Tax is required for the transforming potential of HTLV-1. Loss of Tax expression in HTLV-1-transformed Rat-1 cells resulted in an inability to form tumors and restoring Tax expression restored the tumorigenic potential of these cells, indicating that Tax is required to establish transformation [38]. In combination with *ras*, Tax is sufficient to transform primary rat embryo fibroblast cells in culture and to induce tumors in nude mice. Tax alone can transform Rat-2 cells and induce tumors in athymic mice [41]. These studies demonstrated that HTLV-1 is a transforming retrovirus with a broad transforming potential not limited to primary T cells, and that Tax is necessary and sufficient to transform cells *in vitro* and induce tumor formation *in vivo*.

3. Characterization of Tax-induced tumors in transgenic mouse models

To determine whether Tax plays a role in HTLV-1 induced leukemia/lymphoma, first generation transgenic mouse models expressing Tax under the control of the HTLV-1 LTR were developed, resulting in broad expression of Tax in tissues including thymus, lung, and brain [35]. Interestingly, these mice developed neurofibromas and mesenchymal tumors with visual tumors on the ears, feet, and tail, instead of T cell derived lymphoid tumors, indicating that Tax expression driven by the HTLV-1 promoter leads to neurotropic associated tumor development in this model [35]. To generate a mouse model that more closely recapitulates ATLL, second generation transgenic mice expressed Tax under control of the human granzyme B (GzmB) promoter, which limits transgene expression to $CD4^+$ and $CD8^+$ T lymphocytes (T), natural killer (NK), and lymphokine-activated killer cells [42]. These GzmB-Tax mice developed T-cell lymphomas that expressed high levels of nuclear factor kappa B (NF-κB) [42]. Antisense inhibition of NF-κB expression resulted in tumor regression suggesting that Tax-dependent tumor formation and regression correlate with NF-κB expression [43]. Although GzmB-Tax mice presented with hepatosplenomegaly similar to ATLL patients, they developed large granulocytic leukemia (LGL) indicative of infiltrating neutrophils, basophils, and eosinophils [42]. LGL tumor cells exhibited antibody-dependent cellular cytotoxicity, a primary function of NK-cells, and did not express T-lymphocyte markers, thus these tumors

were derived from malignant NK cells [42,44]. Although GzmB-Tax mice did not develop T-cell leukemia/lymphoma, this model demonstrated that limiting Tax expression to the lymphoid compartment could drive lymphomagenesis.

Third generation transgenic mice expressed Tax under the control of the Lck promoter, which restricts expression to developing thymocytes [45]. At 10 months of age, Lck-Tax transgenic mice developed swollen and enlarged spleens, livers, and lymph nodes, recapitulating clinical features observed in patients with ATLL, and presented with large mesenteric tumors [45]. These mice displayed skin ulcerations involving infiltration of leukemic cells in to the dermis, and lymphoma cells from these tumors had a "flower-like" morphology consistent with ATLL cells [45]. Engraftment of these tumor cells into SCID mice led to the development of an aggressive and rapidly progressing leukemia resulting in death within 28 days, similar to the aggressive nature of ATLL [45]. Although Lck-Tax mice recapitulate the clinical features of ATLL, isolated tumor cells were $CD25^+$, $CD44^+$, $CD69^+$, but $CD4^-/CD8^-$ double negative, indicating that the lymphomas were derived from malignant transformation of immature T cells [45]. In this model restriction of Tax expression to the T cell compartment produced transgenic mice having clinical features of ATLL however, the absence of $CD4^+$ lymphomas and continued expression of Tax in the tumor cells does not precisely model ATLL in these mice.

HTLV-1 humanized SCID mice (HTLV-1-Hu-SCID) were generated by reconstituting hematopoiesis in non-obese SCID mice using human $CD34^+$ hematopoietic progenitor stem cells (HPSCs) infected with HTLV-1 [46]. Within 12-20 weeks of reconstitution, the Hu-SCID mice developed $CD4^+$ T cell lymphomas with clinical and histopathological features similar to ATLL and Lck-Tax transgenic mice [45,46]. Isolated tumor cells expressed HTLV-1 Gag, CD25, CD4, and CD8 proteins, demonstrating that the tumor cells originated from malignant transformation of mature T cells [46]. Additionally, Hu-SCID mice generated using HPSCs infected with a lentiviral vector expressing Tax (Tax-Hu-SCID) developed monoclonal $CD4^+$ tumors suggesting that reconstituting mice with a human hematopoietic system drives Tax-mediated lymphomagenesis of mature T cells [46]. The HTLV-1 infected Hu-SCID mouse model provides a promising tool with which to assess the development and progression of HTLV-1-induced $CD4^+$ T cell lymphomas.

4. Molecular mechanisms of Tax mediated transformation

4.1. Regulation of CREB and NFκB pathways by Tax

Since multiple studies have shown that Tax is sufficient for cellular transformation and is important for HTLV-1 mediated lymphomagenesis [32-38] much effort has been invested into understanding the molecular mechanisms that drive Tax-mediated transformation and tumorigenesis. Microarray analysis of HTLV-1 infected and Tax transfected cells demonstrated genome-wide changes in cellular gene expression patterns including changes in the expression of genes that control proliferation, cell cycle checkpoints, apoptosis, and transcription, suggesting potential pathways through which Tax might function to modulate normal cellular

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responses [47,48]. Extensive mutational analysis of Tax revealed the presence of a nuclear localization signal, nuclear export signal, and activation domains specific for the NF-κB and cAMP-responsive element binding protein (CREB) pathways [49-51]. Tax does not bind DNA but, interacts with cellular proteins to modulate at least three major transcription factor pathways NF-κB, CREB, and serum response factor (SRF) pathways, of which the CREB and NF-κB pathways have been most extensively studied [52-62] and shown to be essential for Tax-mediated transformation.

Modulation of the CREB pathway by Tax is important for transcriptional activation of the HTLV-1 promoter (LTR). The HTLV-1 LTR contains three non-palindromic 21-bp repeats called Tax responsive elements (TRE). Each TRE contains a core CRE sequence flanked by GC-rich sequences, which are required for Tax-mediated transactivation. Under normal physiological conditions, CREB activation is initiated by growth factor stimulated phosphorylation of the kinase inducible domain (KID) of CREB followed by CREB dimerization and recruitment of the CREB binding protein (CBP) through its KID interaction KIX domain [63,64]. The CBP-CREB complex then binds to palindromic CREs to activate transcription of CREB-dependent genes. In Tax expressing cells, Tax interacts with CREB to enhance CREB dimerization and selectively increase the binding affinity of CREB for the viral TRE, which is mediated by the flanking GC rich regions [65-67]. Tax also interacts with the KIX domain of CBP and its homologue p300 to enhance their recruitment to the Tax-CREB-TRE ternary complex, thereby stabilizing the complex and activating viral gene expression in the absence of CREB phosphorylation [67-71]. Thus, Tax can bypass cAMP signaling mediated activation of CREB and induce preferential binding of CREB to the viral LTR rather than to cellular CREs. These results emphasize the importance of the CREB pathway for viral gene expression [54,66,70,70,71,71]

Tax regulation of cellular gene expression through the NF-κB pathway results in cell proliferation, resistance to apoptosis, and maintenance of malignant transformation. In a resting cell, NF-κB is sequestered in the cytoplasm in an inactive complex with inhibitor of kappa B (IκB), which prevents activation of NF-κB -dependent genes [72]. External growth factor stimulation initiates a signaling cascade that induces phosphorylation of IκB by IκB kinase (IKK), resulting in ubiquitination, and subsequent degradation of IκB, which then releases NF-κB to translocate to the nucleus and activate NF-κB-dependent gene expression. Tax disrupts NF-κB regulation by several mechanisms. First, cytoplasmic Tax increases phosphorylation and subsequent degradation of IκBα by forming a ternary complex containing NF-κB essential modulator (NEMO), IKKγ, Tax, and PP2A that blocks deactivation of IKK [73-76]. Constitutively active IKK results in persistent IκB degradation and translocation of NF-κB to the nucleus. Second, nuclear Tax interacts with NF-κB on promoters resulting in constitutive activation of NF-κB dependent genes [77,78]. Persistent degradation of IκB and constitutive activation of NF-κB dependent genes leads to persistent activation of the NF-κB pathway in HTLV-1 infected, and Tax-expressing cells [79]. Upregulation of NF-κB-dependent genes including, but not limited to key T cell activators (IL-2, high affinity IL-2R alpha subunit, and IL-15) is required for immortalization and survival of HTLV-1 transformed cells, setting the stage for neoplastic conversion of a normal T cell [53,60,80]

4.2. CREB and NF-κB pathways in Tax-mediated transformation

A Tax mutant (M47) that is defective for activation of CREB-dependent genes did not induce loss of contact inhibition or anchorage independent growth in Rat 2 cells and failed to induce tumors in nude mice [36], suggesting that activation of the CREB pathway is required to establish Tax-induced tumors. In the same study, a Tax mutant (M22) that is defective for NF-κB activation did transform Rat 2 cells in vitro and induce tumors in athymic mice similar to wild-type Tax, indicating that NF-κB activation is not required to initiate Tax-mediated tumorigenesis [36]. In a different study, a *herpesvirus saimiri* vector carrying the Tax S258A mutant that is defective for NF-κB activity, retained the ability to immortalize PBMCs, which is a prerequisite for transformation [81]. However, a Tax mutant (M319) that fails to activate CREB dependent genes comparable to Tax M47 induced anchorage independent growth in Rat-1 cells and tumor formation in nude mice, suggesting that CREB activation is not required for transformation [82]. Differences between the effect of CREB mutants in this study and the previous study may be due to differences in the specific cell lines and Tax mutants used in the studies. However, since NF-κB mutants retained transforming ability in both studies, and since ablation of NF-κB expression in established Tax tumors led to tumor regression, there is strong evidence that NF-κB is required for tumor maintenance, but not for tumor induction [43]. Analysis of the roles of the CREB and NF-κB pathways in Tax mediated transformation reveal complex effects on tumor initiation, and maintenance. Taken together, the effects of Tax on, NF-κB, IκB, CREB, and CBP/p300 appear to commit a normal cell to a highly proliferative state, setting the stage for the development of ATLL (Figure 1).

5. Effect of Tax on genome stability

5.1. Disruption of DNA repair pathways by Tax

DNA repair and cell cycle progression are tightly linked and involve multiple overlapping pathways that ensure error-free inheritance of genetic material. If a cell incurs extensive DNA damage that cannot be repaired, it will undergo apoptosis or enter a state of replicative senescence. Tax disrupts DNA repair by modulating the functions of key DNA repair enzymes and disrupting the DNA damage response (DDR), resulting in an increased mutation frequency in Tax-expressing cells [83,84]. Cellular DNA damage is repaired by four functionally overlapping pathways that respond to different types of DNA alterations; mismatch repair (MMR) base excision repair (BER), nucleotide excision repair (NER), and double strand break repair (DSBR) [85]. The suppression or disruption of BER, NER or DSBR by Tax appears to contribute to its cellular transformation activity.

BER is initiated by a glycosylase that recognizes helical distortions and flips out the base promoting recruitment of a major repair enzyme, DNA polymerase beta (pol β) [86,87]. Tax has been shown to repress pol β transcription [88,89]. The decreased availability of pol β would reduce the efficient repair of DNA lesions that arise from reactive oxygen species and depurination events consistent with increased mutagenesis of the host genome.

The NER pathway preserves genome stability by scanning for and repairing UV- and chemically-induced bulky adducts [85]. Proliferating cell nuclear antigen (PCNA) is a trimeric sliding clamp that assists in DNA synthesis during DNA replication and repair, by increasing the processivity of DNA polymerase delta (pol δ) to fill in the gap after lesion excision [85,90,91]. In the presence of DNA lesions, elevated levels of $p21^{Cip1/waf1}$ interact with PCNA to block DNA replication without blocking PCNA-dependent DNA repair [92]. Tax activates PCNA gene expression [93], which may allow Tax-expressing cells to overwhelm the $p21^{Cip1/waf1}$-induced replication block and continue DNA replication in the presence of damage, resulting in misincorporation of DNA nucleotides [94,95]. Thus, Tax appears to suppress NER and promote genome instability by increasing the cellular mutation rate.

Unlike NER and BER, less is known about effects of Tax on the DSBR pathway. Double strand DNA breaks (DSBs) are sensed by ataxia telangiectasia mutated (ATM) kinase, which phosphorylates downstream DNA damage checkpoint regulators such as H2AX, Chk2, p53, Nbs1 and MDC1 that function together to arrest the cell cycle and repair DNA [96]. ATM signaling also promotes the recruitment of Ku70 and Ku80 hetereodimers to free DNA ends to facilitate DNA end joining. Tax has been shown to repress Ku80 gene expression, which may impact the cell's ability to recognize and repair free DNA ends [97,98]. In addition, the phosphorylation of ATM targets (H2AX, Chk2 and Nsb1) and ATM autophosphorylation is reduced in Tax-expressing cells, which attenuates the DDR, causing these cells to be released from the S-phase checkpoint while DSBs remain [99-101]. Cells that undergo mitosis in the presence of DSBs frequently form micronuclei (MN), which are markers of genome instability and interestingly, Tax-expressing cells exhibit significantly more micronuclei than control cells [101]. Since, the response to DNA damage and the initiation of DNA repair are tightly linked, the effect of Tax on early cellular processes such as ATM-mediated DNA damage signaling, translates to defects in later processes including cell cycle checkpoints and DNA repair, creating an environment that promotes cellular transformation as shown in Figure 1.

5.2. Impact of Tax on cell cycle regulation

Under normal conditions, eukaryotic cells undergo growth and division resulting in the passage of genetic information, which is essential for survival. Eukaryotic cell division is controlled by four distinct phases: cell growth (G_1, and G_2), DNA synthesis (S), and mitosis (M). Critical cell cycle checkpoints (G_1/S, G_2/M, and M) can be activated to block cell cycle progression and ensure accurate DNA replication and chromosome distribution. Specific complexes containing cyclins, cyclin-dependent kinases (CDK), CDK inhibitors (CKIs), and tumor suppressor proteins work together to maintain genome integrity and prevent uncontrolled proliferation.

Prior to entering G_1, mitogenic stimulation increases the levels of type D (D1, D2, and D3) and E (E1, E2) cyclins. During early G_1 of a normal cell, active D-CDK4/6 complexes phosphorylate the tumor suppressor retinoblastoma (Rb), allowing release of transcription factor E2F and subsequent activation of S phase genes [102]. At this stage, cells are committed to entering S phase where the E-CDK2 complex phosphorylates substrates needed for S phase. Tax expression accelerates progression through G_1 by activating the

transcription of genes encoding D cyclins, which directly interact with D-CDK4/6 to enhance Rb phosphorylation [103-105]. Following its release and translocation to the nucleus, E2F interacts with Tax to transcribe E2F-dependent S phase genes [103]. These transcriptional effects, and modulation of CDK complexes propel Tax-expressing cells through G_1 and force early entry into S phase [104-106].

During the transition from G_1 to S, cells pass through a checkpoint regulated by p53. The tumor suppressor p53 protects cells from transformation by activating the expression of cell cycle control proteins [107] that mediate cell cycle arrest or apoptosis in response to various cellular stresses, including DNA damage. In the presence of DNA damage, p53 arrests the cell cycle by activating the CKI $p21^{waf1/cip1}$, which binds and inactivates CDK2. Therefore, overexpression of $p21^{waf1/cip1}$ induces cell cycle arrest and prevents progression into S-phase until DNA is repaired. $p21^{waf1/cip1}$ also binds to and stabilizes the cyclin D-CDK4/6 complex, leading to increased kinase activity and cell cycle progression, which is consistent with $p21^{waf1/cip1}$ overexpression in Tax-transfected and HTLV-1 transformed cells [108,109]. In addition, Tax-expressing cells display a shortened G_1 phase followed by early S-phase entry, suggesting that the G_1/S checkpoint is deregulated to avoid $p21^{waf1/cip1}$ induced cell cycle arrest [110]. Tax mediated overexpression of $p21^{waf1/cip1}$ may contribute to transformation by accelerating the progression of cells through G_1 and disrupting the DNA damage-induced G_1/S checkpoint [108,111,112].

Further disruption of the G_1/S checkpoint occurs by Tax-mediated inactivation of p53. Tax and p53 have been shown to directly compete for binding to the coactivator CBP/p300, thus p53-dependent transcription could be compromised in Tax-expressing cells [113-115]. Tax has also been shown to suppress p53 function by inducing hyperphosphorylation of p53 at Ser_{15} and Ser_{392}, preventing p53 from interacting with the basal transcription machinery [116,117]. In supporting studies, Tax mutants defective in NF-κB activation failed to suppress p53-mediated transcription [117,118]. Thus, the transcriptional activity of Tax affects p53 regulation of cell cycle checkpoints, DDR and DNA repair, thereby altering the cell's response to internal and external stress stimuli.

Although p53 and $p21^{waf1/cip1}$ prevent unchecked proliferation and genome stability, additional CKIs prevent replication of damaged DNA by inhibiting cyclin-CDK interactions [119,120]. Tax regulates the function of cyclin-CDK complexes by disrupting the inhibitory activities of CDK4 (INK4) inhibitors $p15^{INK4b}$ (p15), $p16^{INK4a}$ (p16), $p18^{INK4c}$ (p18), and $p19^{INK4d}$ (p19), which share overlapping functions to regulate G_1 entry and progression. Before entering G_1 external anti-growth factors such as transforming growth beta (TGF-β) can stimulate cell cycle exit by inducing the binding of p15 to D-CDK4/6 complexes, thereby promoting the degradation of D cyclins [121]. Because a decrease in active D-CDK4/6 complexes prevents cell cycle progression, cellular mechanisms to promote cyclin D overexpression could antagonize p15-mediated arrest. Specifically, the overexpression of D-cyclins and $p21^{waf1/cip1}$ in Tax expressing cells correlates with increased cell proliferation, consistent with cell cycle progression in the presence of ge-

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nome instability. Tax also binds to p16 and suppresses its inhibitory function by allowing cyclin D1 to form active complexes with CDK4/6. Inhibition of p15 and p16 by Tax increases the pool of active D-CDK4/6 complexes resulting in continuous Rb phosphorylation and leading to S phase entry [122,123]. Lastly, Tax represses transcription of $p18^{INK4c}$, and $p19^{INK4d}$, again linking Tax-mediated transcription with cell cycle deregulation [112,122-125]. Cumulative effects of Tax on the G_1 and the G_1/S checkpoints contribute to Tax mediated transformation by continuously promoting cell growth and proliferation in the absence of growth factors.

During S phase, cyclin A-CDK2 begins to accumulate after the G_1/S transition, and is required both to complete S phase and to enter and exit from M phase. HTLV-1 infected cells express low levels of cyclin A because Tax represses cyclin A transcription in a CREB-ATF-dependent manner [126]. Reduced cyclin A levels also promote early egress from mitosis and disrupt the G_2/M checkpoint, producing the types of chromosomal abnormalities observed in ATLL and HTLV-1 transformed cells [127-135].

When cells sense DNA-damage prior to mitosis the G_2/M DNA-damage checkpoint is activated through two DNA damage sensors ATM and ATR, which phosphorylate downstream effectors such as p53, and checkpoint kinases 1 and 2 (Chk1 and Chk2). These downstream effectors phosphorylate downstream substrates to induce cell cycle arrest. Following DNA damage, phosphorylation of Cdc25A by Chk1 targets it for proteasomal degradation, thereby inhibiting activation of the Cdk1/2 complex, which is required to progress through the S and G_2/M checkpoints. Chk1 also phosphorylates p53 and CDC25A/C to induce G_1 and G_2/M arrest, respectively. In response to gamma irradiation, Tax interacts with Chk1 and inhibits its kinase activity, thereby disrupting the G_1 and G_2/M checkpoints and allowing cells to proceed to mitosis in the presence of DNA damage [136]. Interestingly, Tax prevents the release of Chk2 from chromatin after activation by ATM/ATR, thereby preventing phosphorylation of downstream effectors like p53 [137]. Tax disruption of cell cycle regulation and abrogation of the DNA damage response contributes to the proliferation of cells containing DNA damage.

After transiting the G_2/M checkpoint, the cell encounters one last critical checkpoint known as the mitotic spindle checkpoint (MSC). The MSC regulates cell cycle transition from metaphase to anaphase, and its disruption is associated with altered chromosome structures and numbers [138]. HTLV-1 infected/transformed cells and ATLL cells display chromosomal abnormalities including deletions, insertions, rearrangements and translocations, suggesting that Tax disrupts the MSC [127-135,139,140]. The direct interaction of Tax with MAD-1 and APC interferes with proper chromosome alignment along the metaphase plate resulting in the potential loss or gain of genetic material and early exit from mitosis [141,142]. The intimate linkage between the DDR and DNA repair expands the effects of Tax on normal cell proliferation by targeting cell modulators, such as p53, that function in multiple cellular processes.

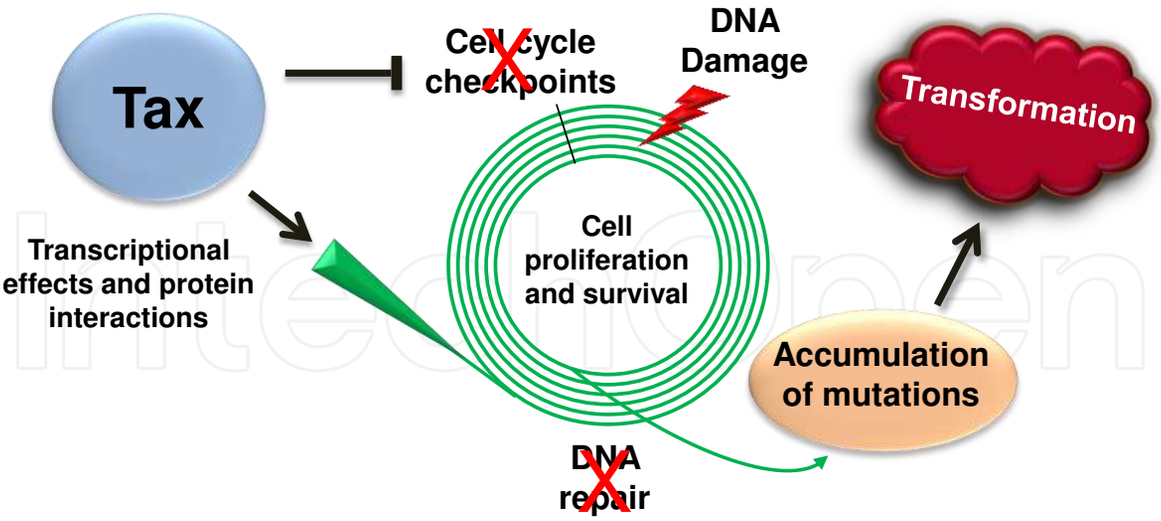

Figure 1. Effects of Tax contribute to cellular transformation: Tax dysregulates cellular gene expression by interacting with cellular proteins and modifying their functions. In the presence of DNA damage (red bolt) Tax interacts with cellular proteins to disrupt cell cycle checkpoints and DNA repair. Persistent activation of NFkB responsive genes such as IL-2, IL-2Rα, and BCL2 drives T cell proliferation and survival. Over many rounds of DNA replication Tax-expressing cells accumulate mutations and promote genome instability, leading to cellular transformation.

6. Conclusions and perspectives

The progression from HTLV-1 infection to the development of ATLL is complicated and not fully understood. The long clinical latency between infection and disease progression makes HTLV-1 an interesting and useful model in which to study multistep oncogenesis [143]. After initial infection, viral proteins including Tax promote viral replication and aid in virus dissemination. HTLV-1 manipulates normal cellular processes to ensure successful replication of the viral genome, which requires entry into and completion of S phase of the cell cycle. Tax inactivates tumor suppressors, interacts with cellular proteins to deregulate cellular gene expression and cell cycle regulation, and inhibits the DDR and apoptosis, all in an effort to disable cell cycle checkpoints and promote cell cycle progression regardless of long-term consequences to the cell (Figure 1). Although the virus remains integrated into the host genome for the life of the host, the virus can successfully replicate and disseminate to other host cells in a matter of days. Thus, accumulation of genetic insults is of little consequence to the virus. Indeed, these insults can be considered an unintended consequence of successful viral replication and dissemination. The ability of Tax to increase the overall cellular mutation rate sets the stage for the development of ATLL. While the effects of Tax on cellular processes are well studied, gaps remain in our understanding of how Tax influences cellular functions due to the interconnectedness of these functions. Advances in animal model systems and experimental systems to study Tax function will help to reveal the complex effects of Tax on interplay between cellular function networks and will increase our ability to identify the key steps involved in HTLV-1 induced leukemogenesis.

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